REMARKS

Applicants have supplied a new abstract which generally tracks the claimed subject matter. Applicants are unable to find a copy of the abstract filed 17 March 2006 either in their own file or in the file history on Public PAIR. However, if the presently proposed abstract is satisfactory, this is not an issue.

Claim 119 has been amended to correct a typographical error. Claims 116 and 120 have been amended to change "comprise" to "consist essentially of" in order better to describe the invention. Claim 116 has been amended to delete "equimolar amounts", and substituted "at the same abundance" as supported in the specification on page 23, lines 36-40. The remaining amendments are to provide antecedent basis and use consistent language. No new matter has been added and entry of the amendment is respectfully requested.

Formal Matters

The replacement abstract is believed consistent with the specification as filed. The wording of claims 116 and 120 has been amended to refer to "cells" instead of "the cell" and the remaining language in these claims has been conformed. In claim 117 "said organism" has been changed to "an organism."

It is believed that the submitted abstract and the proposed amendments dispose of the formal matters in the present Office action.

A new Declaration and Oath has been requested in copending applications due to a strikeover informality. A new Oath is included in this case as well for purposes of consistency.

The Rejection Under 35 U.S.C. § 112, First Paragraph, Written Description

First, the Office objects to the term "comprising" as putatively including things other than the SARM and SSRM employed to effect silencing. It is believed this aspect of the rejection is obviated by substituting "consist essentially of" for "comprise."

The Office then asserts that although double-stranded short RNA molecules (SRMs) are not claimed specifically, claims to SRMs which are collectively short sense RNA molecules (SSRMs) and short antisense RNA molecules (SARMs) are not in compliance with the written description requirement because double-stranded SRMs are included in the genus. Respectfully, this is not the law. Claims to a genus need not disclose, specifically, every member of that genus or even demonstrate that any particular species was contemplated.

This is illustrated beautifully in the holding in *Amgen, Inc. v. Hoechst, Marion Roussel*, 314 F3d 1313, 65 USPQ2d 1385 (Fed. Cir. 2003). Among the many claims at issue were those in U.S. patent 5,756,349. One claim was to a process for producing erythropoietin comprising the step of culturing, under suitable nutrient conditions, vertebrate cells according to previous claims. The broadest previous claim describes the cells as being capable of producing erythropoietin in the medium in excess of 100 units per 10^6 cells in 48 hours and comprising non-human DNA sequences that control transcription.

The whole application of *Amgen* in support of this claim described only the cloning of the gene for erythropoietin and producing erythropoietin by introducing an exogenous cloned gene into vertebrate cells. The accused infringer, however, produced erythropoietin in vertebrate cells by using the endogenous erythropoietin gene but supplying it with a stronger (non-human) promoter.

The accused infringer's method was held to be a species that fell within the scope of the claims as written. It is quite clear that the accused infringer's approach was not envisioned by the *Amgen* inventors when the application was filed. In fact, the *Amgen* specification said that the invention was "uniquely characterized" by host cell's expression of "exogenous DNA sequences." The claim was challenged based on written description, just as the Office has challenged the claims here. The Federal Circuit held that the written description was adequate. For details, the Examiner is referred to pages 1396-1400 of the copy of the case attached hereto for the convenience of the Office.

It is apparent that this case is precisely on point. There is no need for the applicant to have contemplated every species that falls within a claimed genus in order to provide adequate written support for the claim.

That having been said, in the present case, there is significant evidence from a review of the entire disclosure that the present applicants did provide a description of dsRNA as one form in which the short RNA molecules could be utilized even if the description was not explicit. This is evidenced by the statement that SRMs refers collectively to SSRMs and SARMs; the definition of the nature of the molecules as "short complementary molecules which could base pair with the target RNAs"; the Baulcombe declaration (submitted in copending application 10/013,316 and enclosed herewith) which clarifies that the transgene silencing experiment described on page 24, lines 4-28 had to result in the production of double-stranded species active in inducing silencing; the statement that the discovery of the SRMs of this invention provides evidence that dsRNA induction of silencing in nematodes and the cause of PTGS in plants are related (page 3, lines 24-26); and the statement that whenever a previously uncharacterized species of antisense RNA complementary to

targeted mRNA was detected "corresponding sense RNA molecules were also detected" (page 2, lines 12-20). Therefore, it cannot be concluded that the written description does not contemplate double-stranded RNA molecules as being within the scope of the claims.

For completeness, applicants point out that there is further evidence that species not explicitly described can be included in a generic claim. The availability of a selection invention as was the case in *In re Jones*, 958 F2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992), is determinative. In *Jones*, a prior art patent disclosed and claimed a genus of esters of dicamba, a known acid used as an herbicide. In *Jones'* application, a specific ester that fell within the genus of the prior art patent was found patentable over that disclosure. There was no contention of invalidity of the issued prior art claim; the failure of the patentee to contemplate this specific ester is nevertheless, apparent. Thus, a species falling within a claimed genus does not render the genus claim unpatentable, even if it is evident or could be demonstrated that such species was not contemplated by, or was not specifically or explicitly described by, the applicant.

That this is the policy of the U.S. PTO is also confirmed, for example, by Example 14 of the Written Description Guidelines which permits, for example, a protein to be claimed in terms of a structural limitation such as 95% sequence identity to a disclosed sequence in combination with a functional limitation. Clearly the applicants do not have in mind every embodiment within this class of compounds. Of course, a complete list of all sequences with this homology (quite extensive) could be generated by computer, but it would not be known which of those meets the functional requirements. The Office finds it not necessary for the applicant to have contemplated the specific sequences that will eventually fall within the scope of the claims.

This is apparent just from everyday practice as well. It would be a rare issued patent, for example, that describes with specificity the preparation of every chemical compound that falls within the claimed genus. Concerned scientists consistently review claims to genera of compounds to evaluate whether their individual compound falls within such claims when their individual compound is not described in the specification supporting the genus claim.

The Office asserts that the conclusion that would be drawn by the reader, that at some point the SARM found in plants undergoing PTGS and the SSRM would be a double-stranded form, "does not indicate that the specification at the time of filing contemplated introducing SRMs in double-stranded form into a cell to cause PTGS of a target gene." As demonstrated above, this is not the case, but in any event, does not matter. Applicants are not claiming this as a species of the genus. There is no showing that there is insufficient disclosure to support the claimed genus in the specification.

Next, the Office states that the term "equimolar amounts" is unsupported. This has been replaced by "same abundance" and the support has been pointed out on page 23, lines 36, *et seq.*

In view of the amendment and foregoing discussion, applicants believe the rejection based on lack of written description may be withdrawn.

The Rejection Under 35 U.S.C. § 112, First Paragraph, Enablement

The Office asserts that the claimed method is unworkable based on the paper of Klahre, *et al., PNAS* (2002) 99:11981-11986. The Office asserts that Klahre demonstrates that only double-stranded small molecules that also contain 2- and 3-nucleotide 3′ overhangs could cause silencing and that complete specificity is required. Klahre is said to have shown that 21 nucleotide sense and

22 nucleotide antisense single-stranded nucleic acid molecules could not produce PTGS of their target sequence. The Office acknowledges applicants' previous argument that the method claimed by applicants was never conducted by Klahre and suggests that applicants are obliged to provide an explanation as to why the results of Klahre would be different if their method were performed.

Respectfully, applicants believe that the burden of proof is on the Office to demonstrate that this is the case. There is simply nothing in the art to show that the method of the present claims is unworkable.

Klahre used only either an SSRM alone or an SARM alone or a short double-stranded RNA molecule. This is very different from providing both an SSRM and an SARM which, if they are also complementary to each other, could form a double-stranded DNA molecule either before, during or after introduction into a cell. In addition, as noted above, double-stranded RNA is legitimately included within the scope of the pending generic claims.

With respect to the assertion that Klahre demonstrates only double-stranded small molecules that also contain 2- and 3-nucleotide 3′ overhangs could cause silencing, applicants enclose Chapter 13 from RNAi – A Guide to Gene Silencing, G. J. Hanson, *et al.,* CSHL Press (2003) on mammalian RNA interference, authored by Thomas Tuschl. This chapter cites, on page 278, an article by Paddison, *et al.*, as demonstrating that blunt ended duplexes with up to 29 base pairs are also able to mediate RNA interference in cultured cells. A copy of this chapter as well as of the cited Paddison, P. J. *et al., Genes & Dev.* (2002) 16:948-958 are also enclosed.

In Figure 1, on page 950, figure 1A shows several RNA molecules, including a siRNA with 3′ 2nt overhangs, shRNA's which are blunt ended – cshFf, cshFf-L7 and cshFf-L7m. In figure 1B,

silencing of luciferase is shown for the siRNA, the cshFf and the cshFf-L7, but not for cshFf-L7m. The lack of silencing by the cshFf-L7m is explained by the lack of a contiguous segment of exact complementarity of the dsRNA that is produced from that precursor on contact with dicer (see Paddison, page 950, right-hand column, where it is stated: "the presence of mismatches with respect to the target mRNA essentially abolished silencing potential."

Thus Paddison demonstrates that no overhang is required.

Further, although conducted in a different organism, it has been demonstrated by Martinez, J., *et al., Cell* (2002) 110:563-574 that although single-stranded RNA's are less efficient than double-stranded, they do effect PTGS. A copy of the Martinez paper is also enclosed.

The relevant experiments in Martinez appear on page 569 and were conducted in HeLa cells. In these experiments, single-stranded 5′ hydroxyl and 5′ phosphate modified antisense siRNA's were tested for targeting an endogenous gene in the HeLa cells. As noted at the top of the right-hand column, gene silencing was observed with phosphorylated as well as non-phosphorylated antisense siRNA's ranging in size between 19 to 29 nucleotides. The phosphorylated antisense RNA's were better.

This is supported as well by Zamore, P. D., *et al., Cell* (2000) 101:25-33 (enclosed). See page 29, right column, which describes the effect of single-stranded antisense RNA on mRNA stability – it's effect is roughly half that of dsRNA.

Respectfully, the Office has not provided any document that demonstrates that the method of the invention does not work or would not be expected to work. For this reason, the rejection should be withdrawn.

The Art Rejection

All pending claims were rejected as assertedly anticipated by Fire, *et al.,* U.S. patent 6,506,559. Respectfully, applicants believe that on page 13 of the Office action, Fire has been misinterpreted. The Office states "the method comprises introducing into cells *short* RNA molecules that are complementary and are in sense and antisense orientation with respect to a portion of the target gene sequence. The RNA molecules are at least 25 nucleotides in length." This is a mischaracterization of Fire and is further inconsistent with the characterization of the work of Fire as set forth on page 7 of the Office action which states "the references cited in the specification in support of the induction of PTGS with dsRNA teach induction with double-stranded RNA that are clearly much longer than 20-30 base pairs in length."

The interpretation of Fire set forth on page 7 of the Office action is accurate. There is nothing in Fire that describes using short RNA molecules to effect gene silencing. The only reference to 25 bases is in column 8 at lines 5-6 which says "the length of the *identical nucleotide sequences may be at least 25, 50,...* bases."

Thus, the reference to 25 nucleotides in Fire does not refer to the length of the RNA molecules supplied, but the length of the nucleotide sequence in the longer double-stranded RNA that is required to be identical. It is apparent from the examples in Table 1 of Fire that much longer

RNA molecules are employed. Thus, Fire does not anticipate the invention as claimed and this basis for rejection may be withdrawn.*

Conclusion

The claims have been amended in response to the objections raised based on written description. The document cited as demonstrating lack of enablement fails to disclose that the method as claimed is unworkable, as both sense and antisense RNA molecules are never supplied to the cells employed. The rejection over Fire is shown in error since much longer double-stranded RNA is used as compared to that required by the claims. The Examiner kindly acknowledges this on page 7 of the Office action. Indeed, applicants' contribution to the art is to demonstrate that short RNA molecules, specifically, are responsible for gene silencing.

* It is solely applicants who recognized the effectiveness of short RNA molecules to cause PTGS - the general knowledge in the art assumed that much longer molecules were needed. See, for example, Tuschl, T., *et al, Genes & Dev* (1999) 13:3191-3197 (enclosed). This article was accepted by the journal one day after the priority date to which the present application is entitled. Please see the last paragraph of the right hand column on page 3194, which states that the *in vitro* system of the authors confirmed published *in vivo* results that dsRNA of 49 bp could not effect PTGS and that dsRNA of 149 bp was only slightly effective. Robust results were obtained with dsRNA of 505 and 997 bp. It is only after applicants' *Science* paper was published on October 29, 1999, that it became generally recognized in the art that SRMs were instrumental in PTGS. (See later published papers of this group – *e.g.*, Zamore, P. D., *Cell* (*supra*), acknowledging at page 26, left hand column, that "the 21-23 nt fragments from the dsRNA are targeting the cleavage of the mRNA.").

Applicants thus believe that claims 116-124 should be passed to issue. If minor issues remain that could be resolved by phone, a call to the undersigned is respectfully requested.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicants petition for any required relief including extensions of time and authorize the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket No. 616292000111.

Respectfully submitted,

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